Hepatitis A: Biology, Pathophysiology and Vaccine

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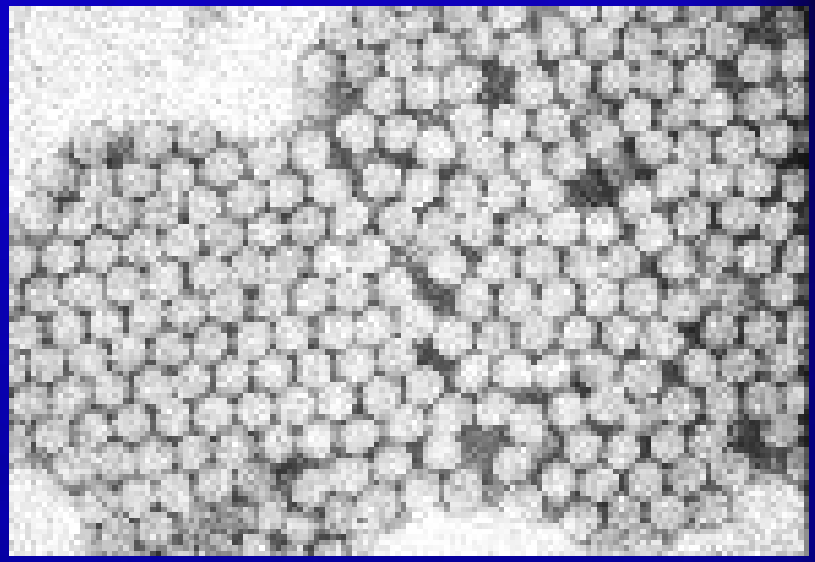
Overview

- Virology
- Epidemiology
- Pathogenesis
- Clinical manifestations
- Diagnosis and management
- Vaccination
- Post exposure prophylaxis

Hepatitis A Virus

- Picornavirus
  - Classified as a hepatovirus, formerly enterovirus 72
- Naked icosahedral RNA
- One Serotype, 4 genotypes
- Single + strand
  - 7848 nucleotides
  - Codes for 4 proteins
  - VP1, VP2, VP3 & VP4



Biology / Virology

- Acid exposure – PH 3
- Thermostable – 60 C for 60 minutes
  - At 85 degrees C – one minute
- Dried feces – room temp – 4 wks (17%)
- Survives in oysters – 5 days (12%)

Biology / Virology
Epidemiology

- 1.5 million cases reported each year
  - Under reported due to the amount of subclinical infections.
- Transmission is through the fecal-oral route
  - Typically contaminated water or food

Biology / Virology
Epidemiology

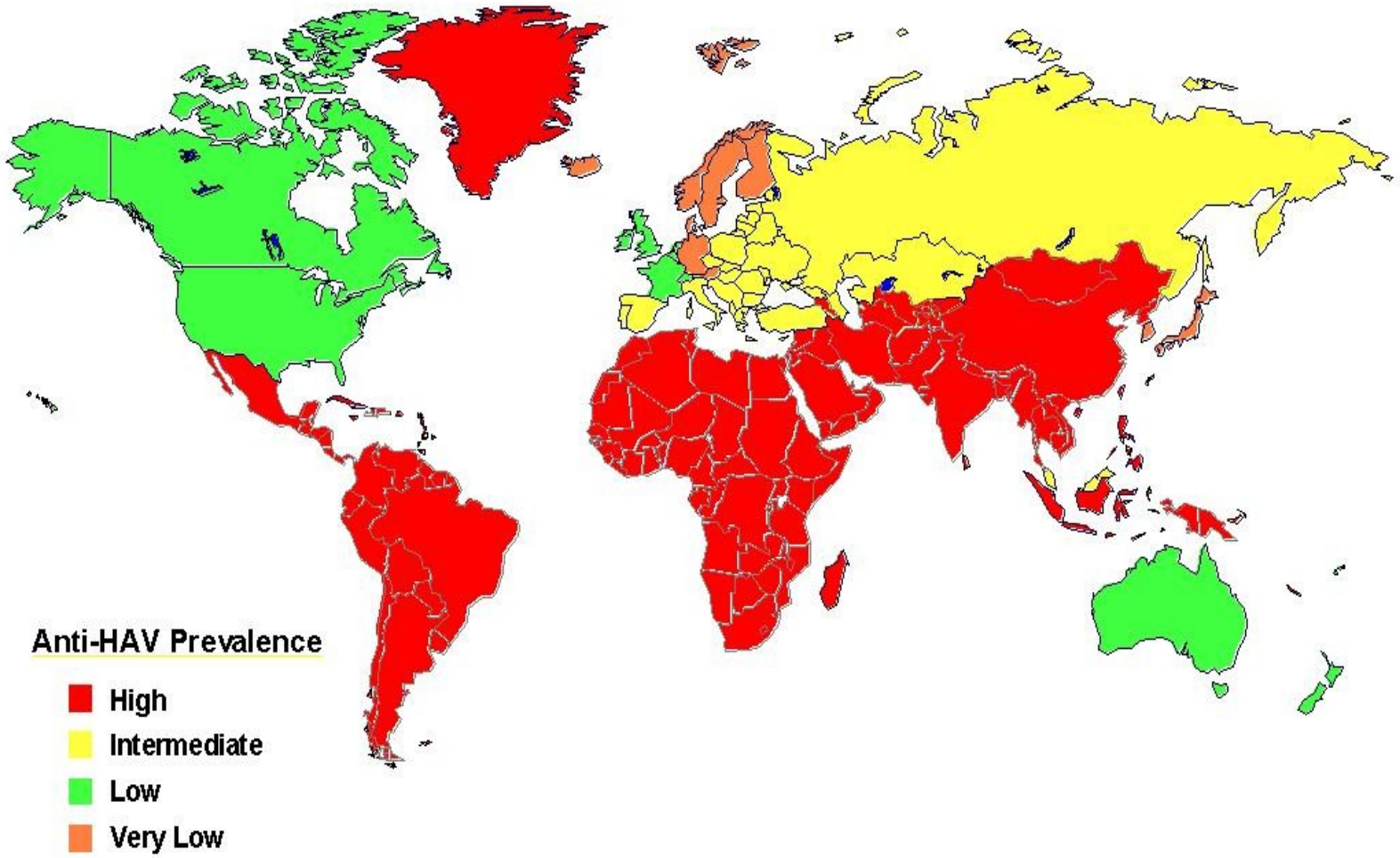
- Shellfish is a common vehicle of spread.
- Shanghai in 1980
  - 300,000 cases traced to contaminated shellfish during a clam festival
- HAV is typically acquired from travel to endemic areas

Maintenance of HAV in the Human Population

- No reservoir in the human population.
- No reservoir of viremic carriers.
- No reservoirs of nonhuman primate carriers.

- HAV depends on serial propagation from infected individuals to susceptibles.

Geographic Distribution of HAV Infection



Modes of Transmission

- Fecal-Oral
  - Household contacts
  - Intimate
  - Institutional
  - Outbreaks from a common source
    - Water
    - Food
    - Molluscs
  - Reports of percutaneous, transfusion related and through IV drug use.

Risk Factors

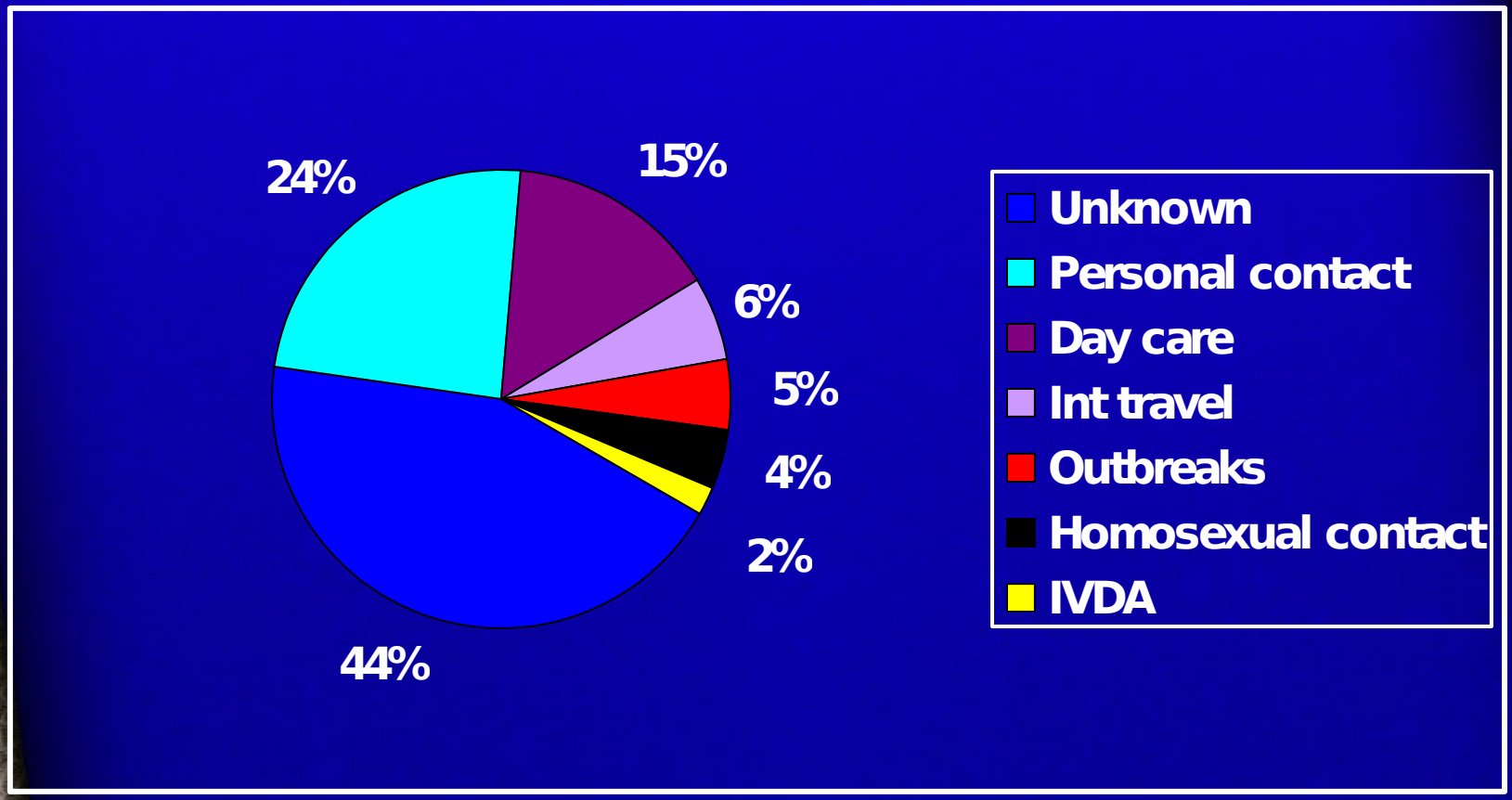
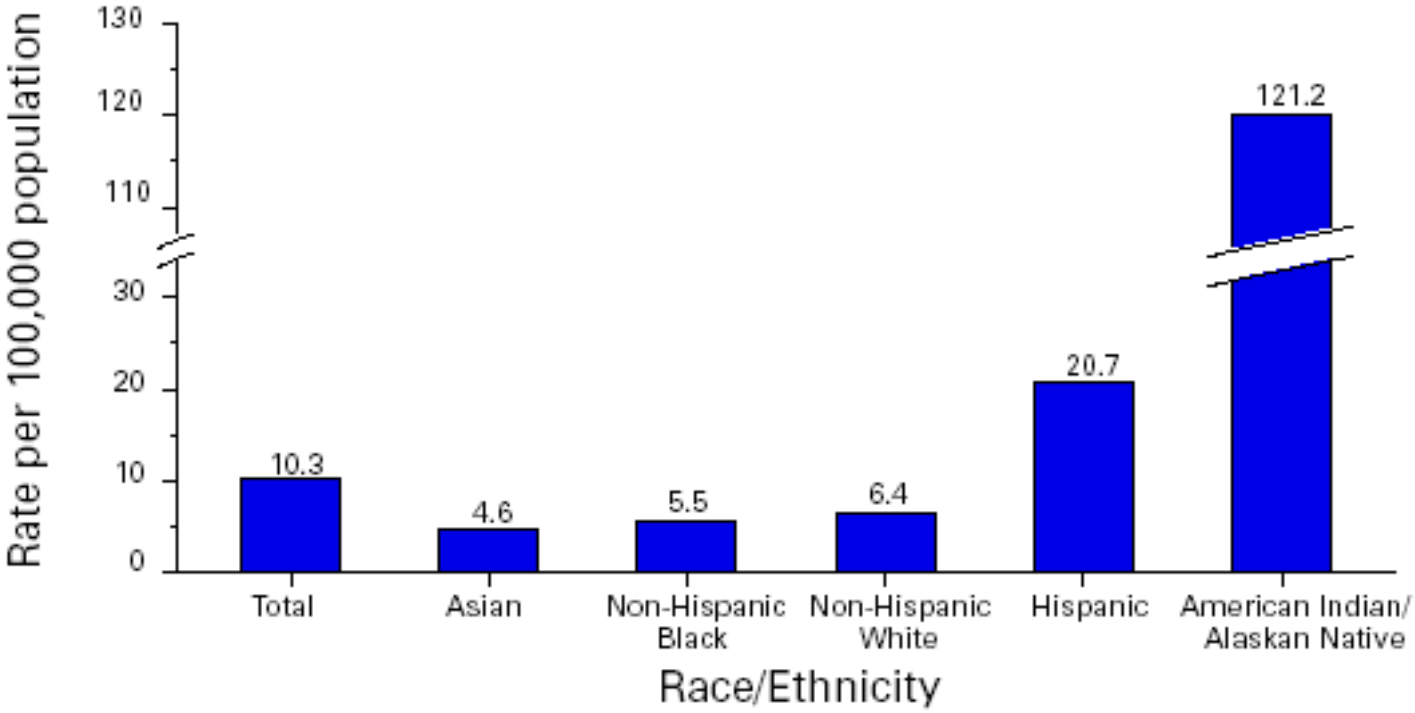


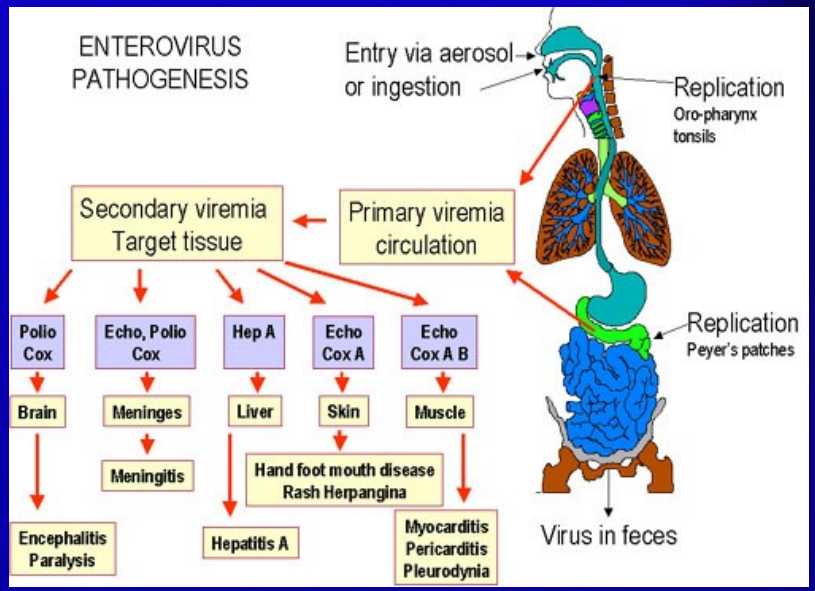
FIGURE 2. Rates of reported hepatitis A, by race/ethnicity — United States, 1994

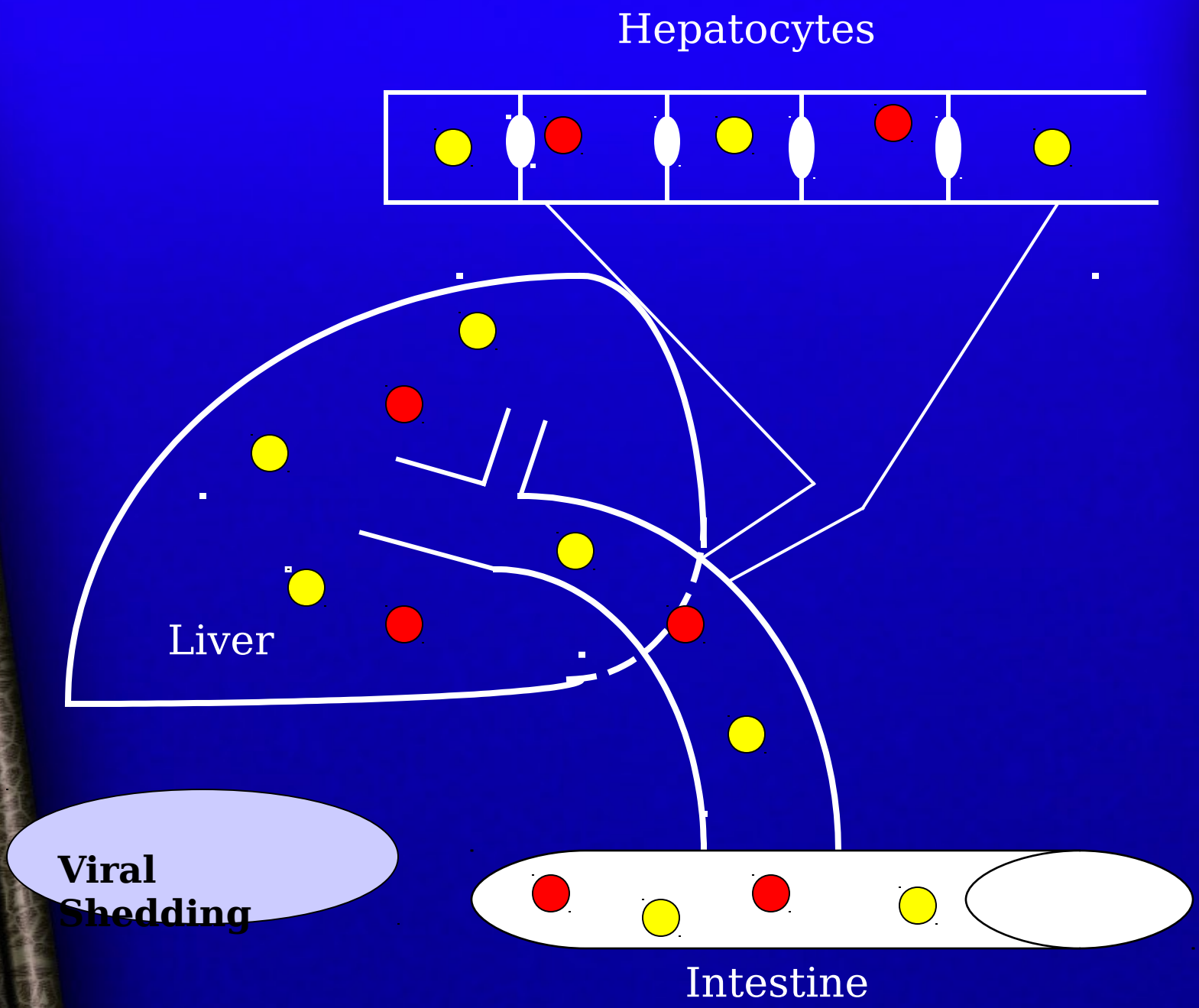


Source: National Notifiable Diseases Surveillance System.

Pathophysiology

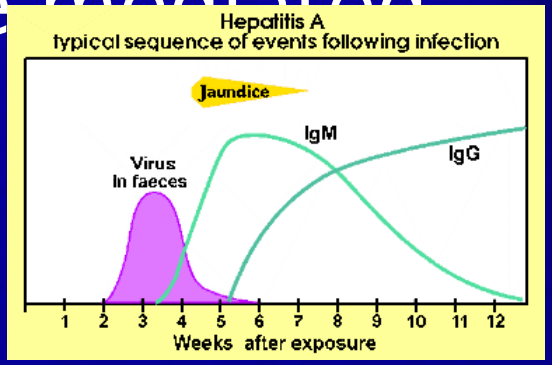
- With fecal oral transmission the virus reaches the liver from the bowel.
- Replication occurs in the hepatocyte. From there it reaches the stool via the bile



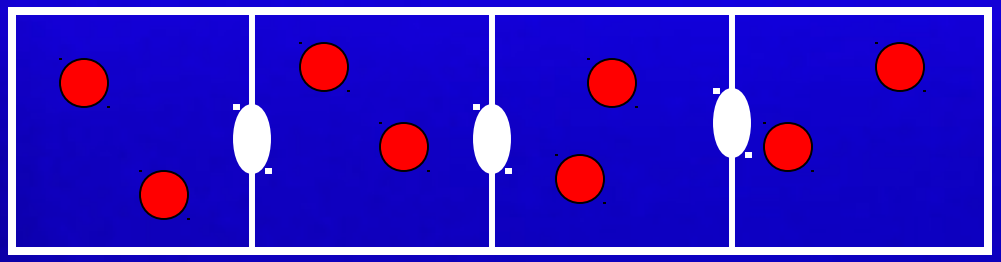

Hepatocytes
Liver
Viral Shedding
Intestine

Pathophysiology

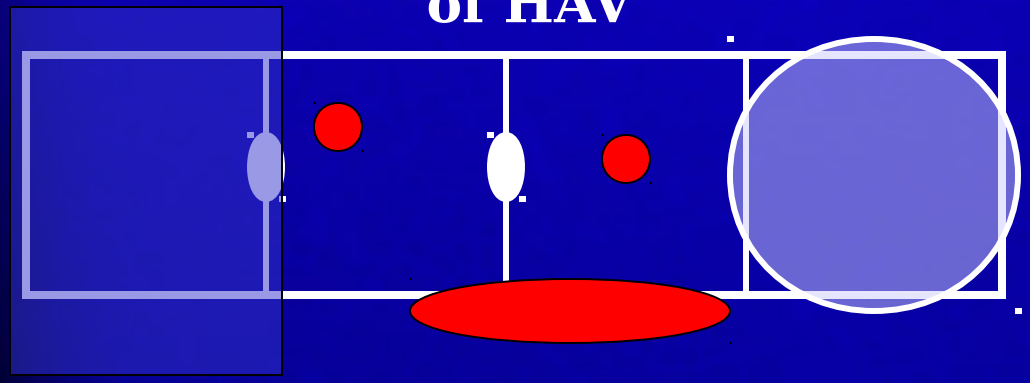
- The virus is not likely to be directly cytotoxic.
  - Early during the incubation period HAV can be found within the hepatocytes without evidence of liver injury.
- The mechanism of injury is postulated to be immune mediated



Replicative Phase of HAV

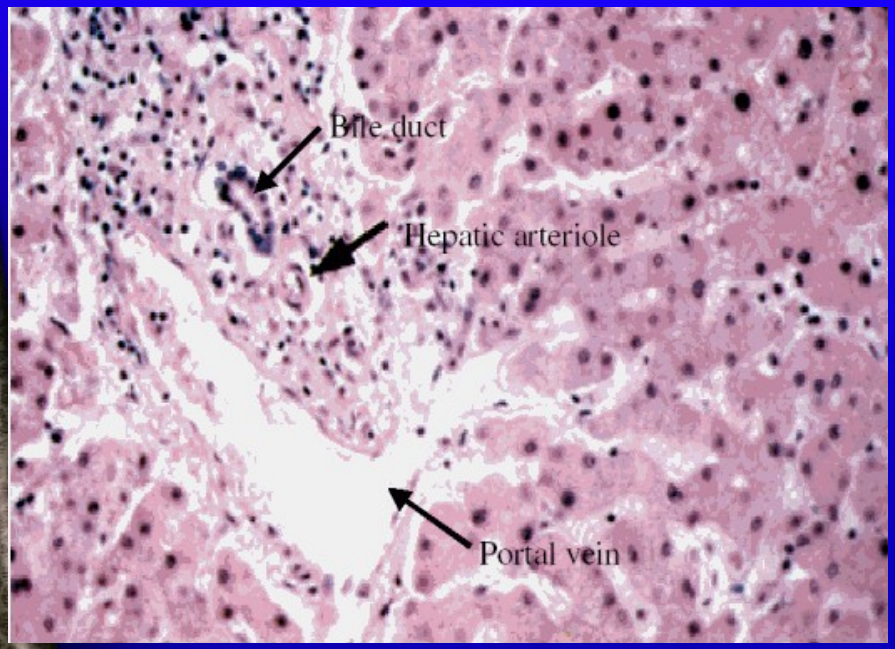


Necroinflammatory phase of HAV

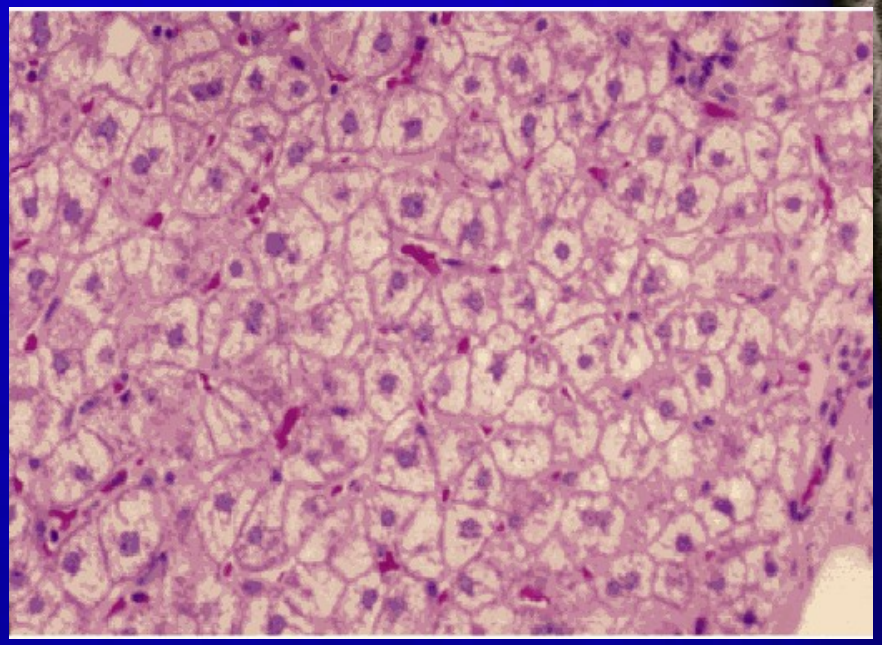


Pathogenesis

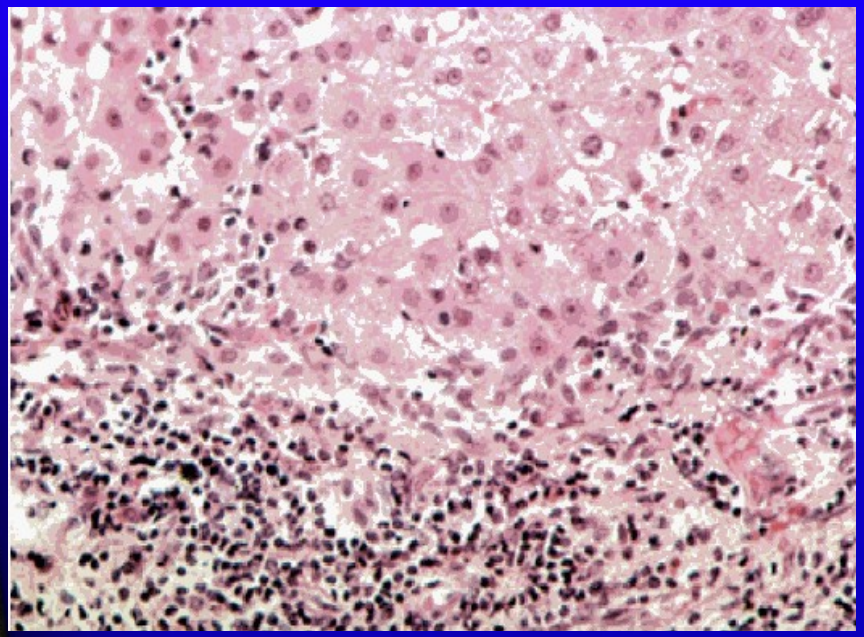
- Pathological changes are common to all types of viral hepatitis
  - Parenchymal cell necrosis
  - Histiocytic periportal inflammation
  - Rarely, in cases of fulminant hepatitis there can be massive necrosis



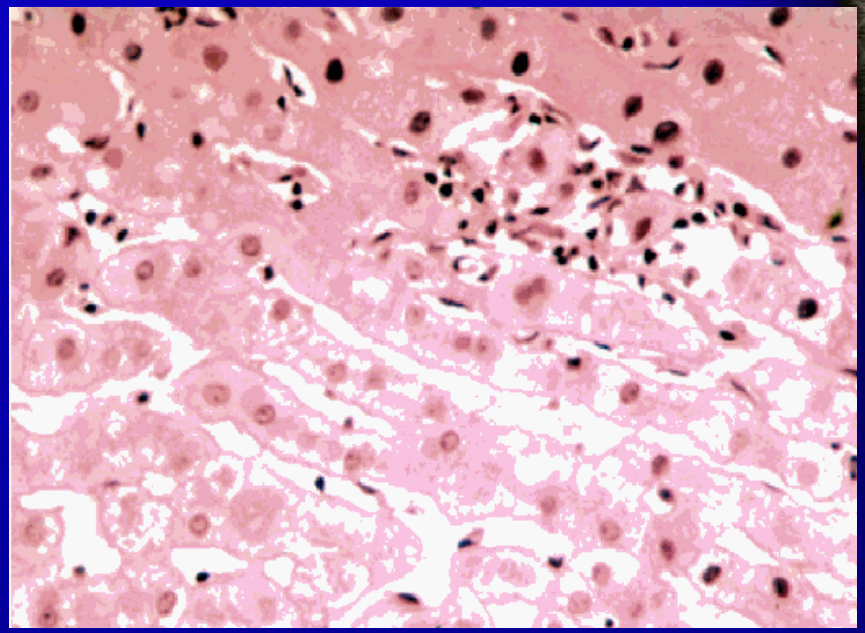
Normal Liver



Balloon Degeneration



Piecemeal Necrosis



Cell Dropout

Pathogenesis

- After ingestion, the incubation period takes an average of 4 weeks.
- As the hepatocytes are destroyed the AST and ALT rise.
- This is the time that patients typically become symptomatic.

Clinical Manifestations

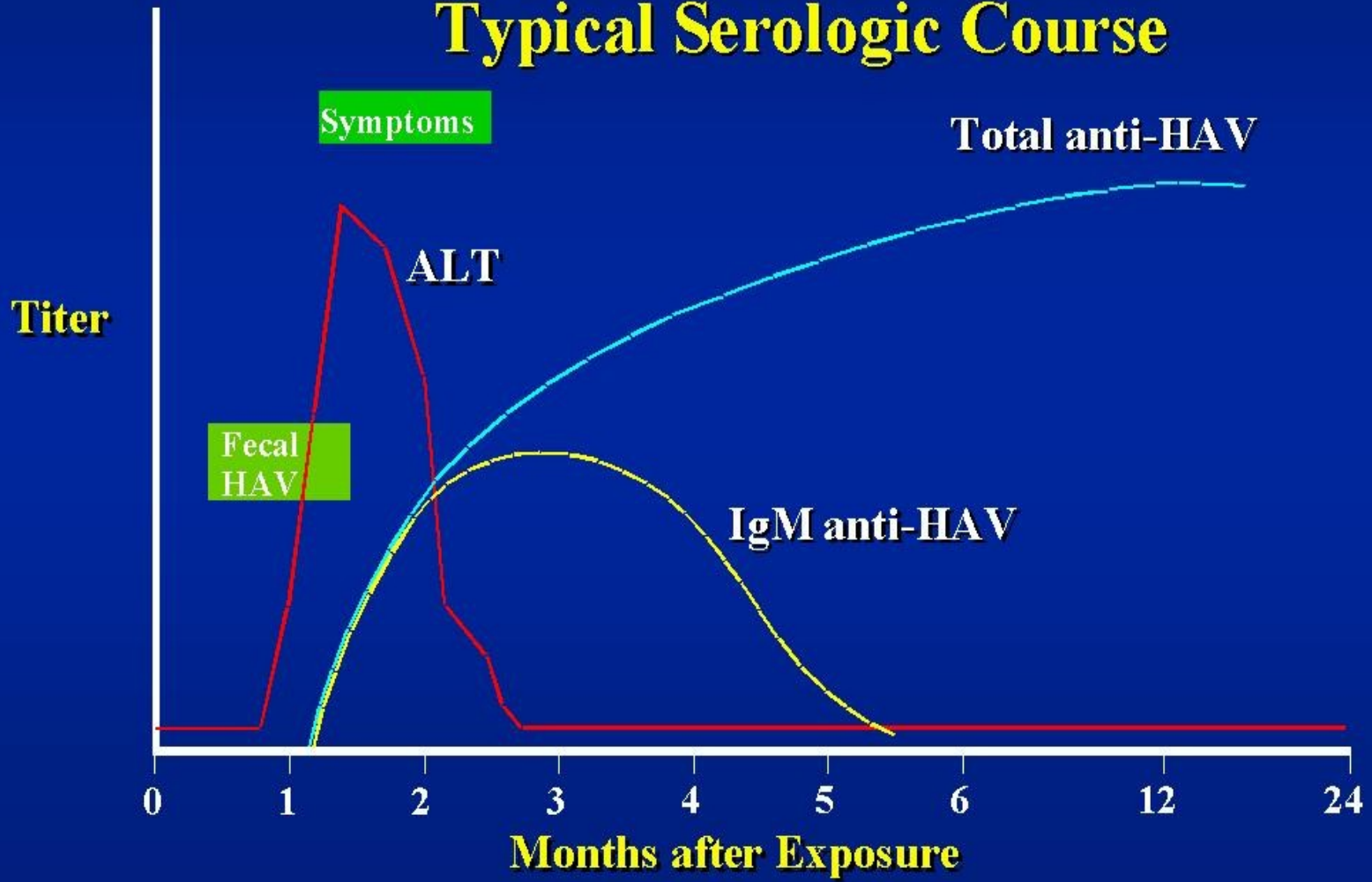
- Prodromal SX's
  - Fever
  - Malaise
  - Weakness
  - Anorexia
  - Nausea and vomiting
  - Arthralgias & myalgias
- Flu like symptoms
  - Pharyngitis
  - Cough
  - Coryza
  - Photophobia
  - Headache

Five clinical patterns.

1. Asymptomatic.
   - No jaundice.
2. Symptomatic.
   - Self limited < 8 weeks.
3. Cholestatic jaundice.
   - 10 weeks or longer.
4. Relapsing.
   - 2 or more acute episodes over 6-10 weeks. 10% of pt's.
5. Fulminant hepatitis.
   - 1-5% of pt's.
   - 55% within the 1st week.
   - 90% within the 1st 4 weeks.
   - If >4 wks something else is the cause.

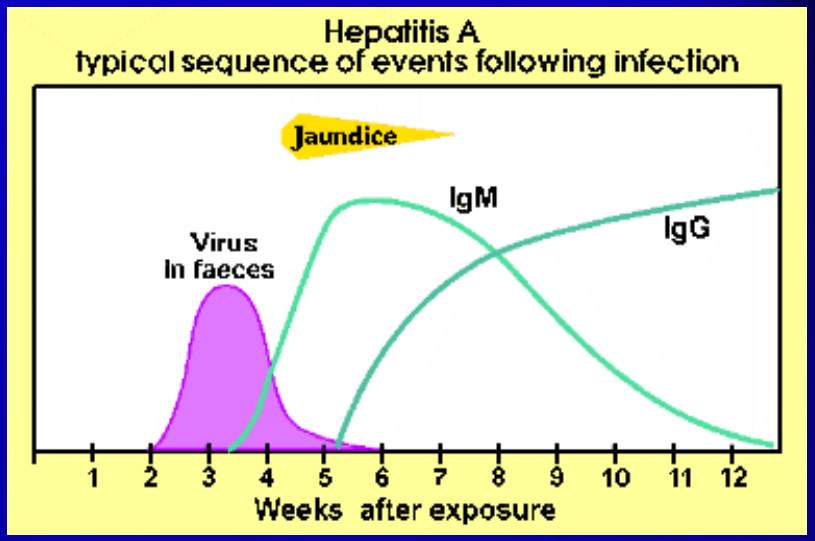
Hepatitis A Virus Infection

Typical Serologic Course



Diagnosis

- Serum IgM is the test of choice.
- EM of the stool has been used
  - Not practical given the low amount of the virus in stool after onset of sx's.
- IgG is reserved for to determine status.



Treatment

- Most patients can be treated at home.
- Bed rest guided by individual sx’s of fatigue.
- No specific dietary recommendations with the exception of prohibition of ETOH during the acute phase.
- Most patients show complete clinical and biochemical recovery within 3-6 Mos.

Vaccine

Prevention

- Prior to 1992.
  - Promotion of hygiene to reduce fecal oral spread.
  - Short term passive immunization.
    - Pre exposure for travel to endemic areas.
- 1992 – 1st available vaccine in Europe.
  - HAVRIX – introduced to the US in 1995.

Prevention

- Vaqta –was introduced in 1996.
- Both vaccines are whole virus preparations.
  - Produced by growth of attenuated HAV in tissue culture.
  - Inactivated with formaldehyde.
  - Stable – storage for up to 2 years at 4 degrees Celsius.

Routine Immunization

- Goals of HAV immunization are
  - Protect persons from infection
  - Reduce disease incidence by preventing transmission
  - Ultimately eliminate transmission
- Children have a high incidence of HAV
  - This makes them a good target for immunization strategy.

Routine Immunization

- Routine childhood immunization would
  - Prevent infection in age groups that account for at least 1/3 of cases.
  - Eliminate a major source of infection for other children and for some adults
  - Prevent infection in all older patients who are vaccinated during childhood

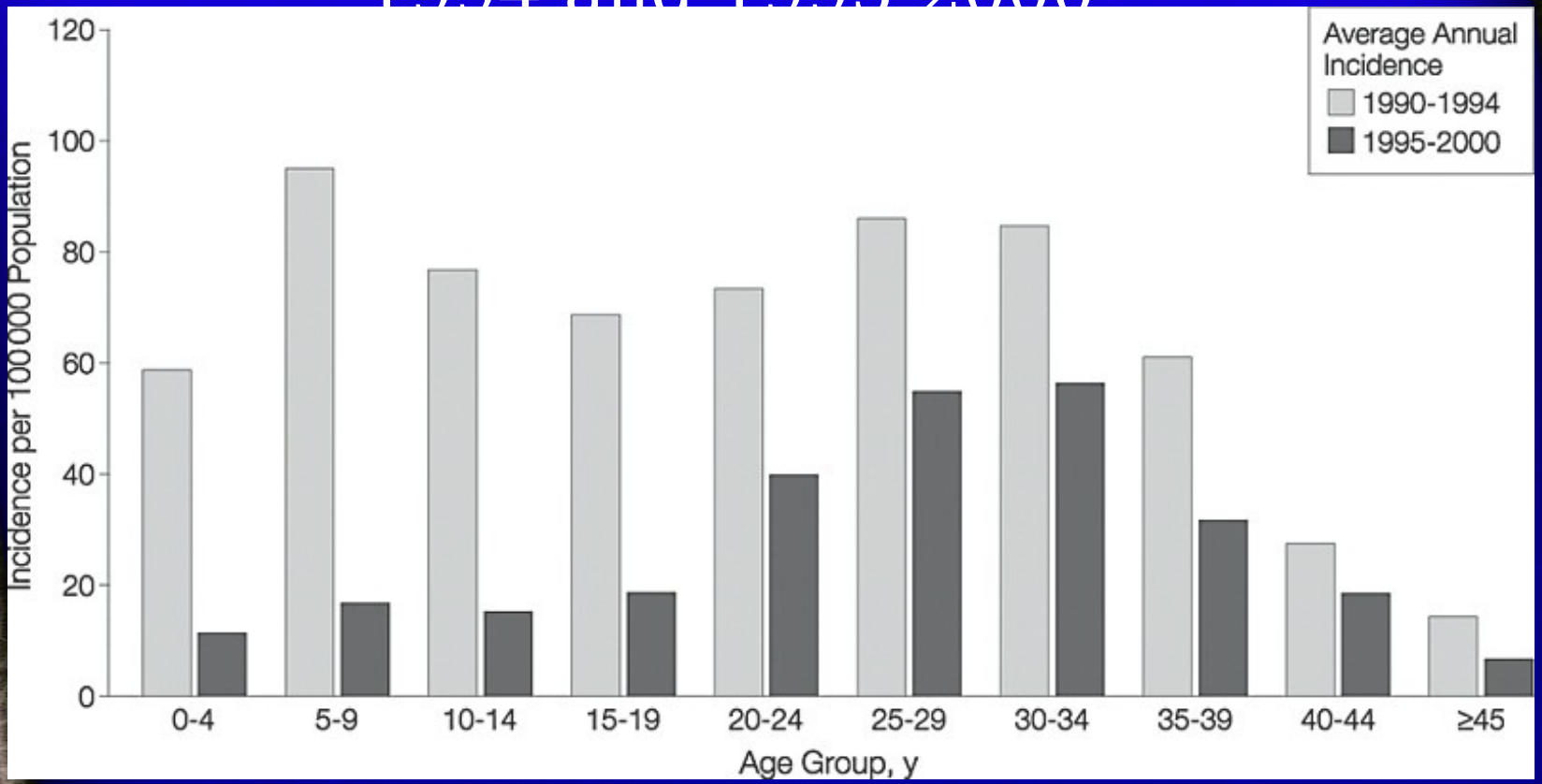
Routine Vaccination of Children

- Averhoff et al. Dec 2001. JAMA
  - Evaluated the effect of routine vaccination of children on disease incidence in a community with recurrent HAV epidemics
  - Jan 95 through Dec 2000 in Butte County, California
    - 29789 of 44,982 (66%) eligible children received one dose of HAV vaccine
    - 17,681 (39%) patients received a second dose

Routine Vaccination of Children

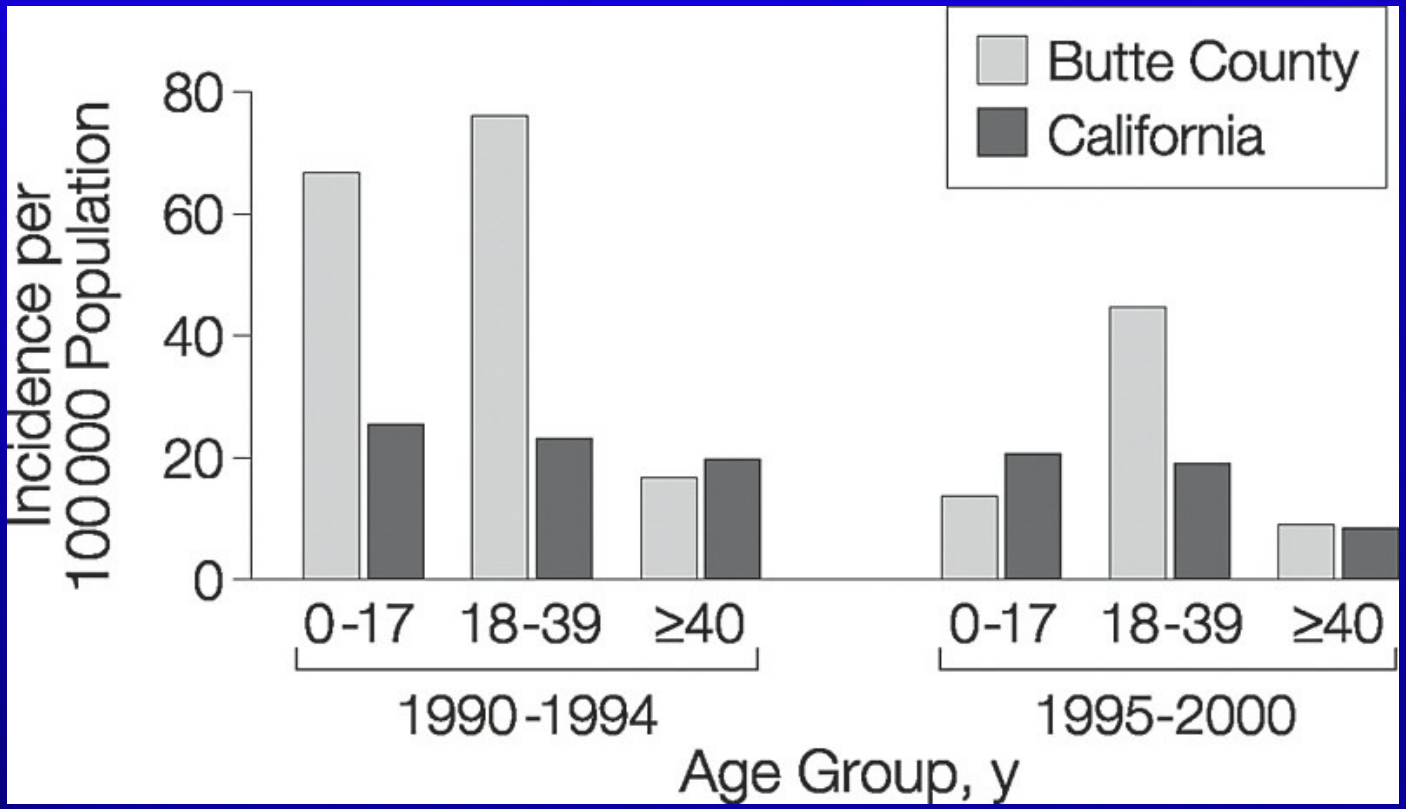
- The number of HAV cases among the entire county population decreased by 93%
  - 57 cases reported in 1995
  - 4 cases reported in 2000
  - Of the 245 cases reported during the 6 year period 40 (16%) occurred in children <17 y/o.
    - 16 of these occurred in 1995, 1 in 2000

Average Annual Age-Specific Hepatitis A Incidence in Butte County, California, 1990-1994 and 1995-2000



Averhoff: JAMA, Volume 286(23).December 19, 2001.2968-2973

Average Annual Hepatitis A Incidence by Age Group for Butte County, California, and All of California, 1990-1994 and 1995-2000



Averhoff: JAMA, Volume 286(23).December 19, 2001.2968-2973

Routine Vaccination of Children

- In Butte County, California
  - Childhood vaccination decreased the incidence of HAV among children and adults and controlled the disease in a community with recurrent outbreaks.

Immunization in Infants

- HAV vaccine is immunogenic in children less than 2 y/o who do not have passively acquired antibodies from the mother
- Due to passive immunization from the mother. Children that receive the vaccine have reduced geometric mean antibody concentrations (GMC's)

Indications for Immunization

- Travel to endemic regions
- Chronic liver disease
- Clotting factor disorders
- Community outbreaks
- 11 States with HAV rates 2x the national average

TABLE 2. Burden of hepatitis A in states with average reported incidence of ≥20 cases per 100,000 population — 1987–1997*

State	Rate (per 100,000)	Cumulative average number of cases per year†	Cumulative percentage of cases	Cumulative percentage of U.S. population§
Arizona	48	1,852	7	2
Alaska	45	2,137	8	2
Oregon	40	3,297	12	3
New Mexico	40	3,916	14	4
Utah	33	4,519	16	5
Washington	30	6,007	21	7
Oklahoma	24	6,786	24	8
South Dakota	24	6,953	25	8
Idaho	21	7,172	26	9
Nevada	21	7,449	27	10
California	20	13,706	50	22

*United States reported disease incidence during 1987–1997 was 10.8 cases per 100,000 population. Reported hepatitis A cases from these 11 states accounted for an average of 50% of reported cases each year, yet the total population of these states represents 22% of the U.S. population.

†Approximately 37% of cases were among persons aged <20 years.

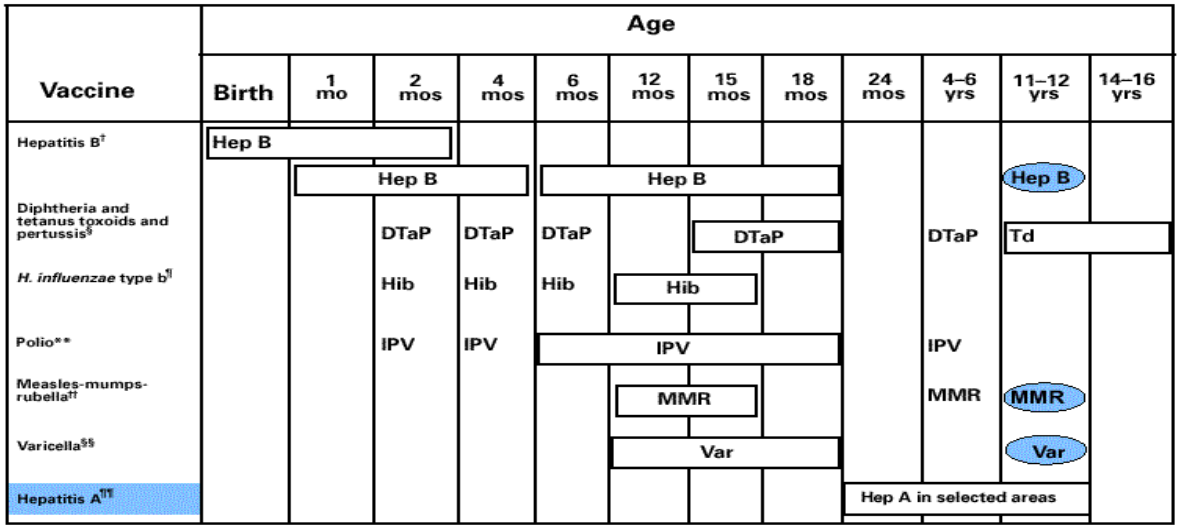
§1997 estimate of the U.S. Bureau of the Census.

Source: National Notifiable Diseases Surveillance System.

Indications for Immunization

- Other categories
  - Military
  - Peace keeping forces
  - IVDA
  - Homosexual behavior
  - Occupational exposure

FIGURE 1. Recommended childhood immunization schedule* — United States, January–December 2000



On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP) recommended that Rotashield® (rhesus rotavirus vaccine-tetravalent [RRV-TV]), the only U.S.-licensed rotavirus vaccine, no longer be used in the United States (*MMWR*, Vol. 48, No. 43, November 5, 1999). Parents should be reassured that children who received rotavirus vaccine before July 1999 are not now at increased risk for intussusception.

* This schedule indicates the recommended ages for routine administration of licensed childhood vaccines as of November 1, 1999. Any dose not given at the recommended age should be given as a "catch-up" vaccination at any subsequent visit when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

† **Infants born to hepatitis B surface antigen (HBsAg)-negative mothers** should receive the first dose of hepatitis B vaccine (Hep B) by age 2 months. The second dose should be administered at least 1 month after the first dose. The third dose should be administered at least 4 months after the first dose and at least 2 months after the second dose, but not before age 6 months. **Infants born to HBsAg-positive mothers** should receive Hep B and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1–2 months and the third dose at age 6 months. **Infants born to mothers whose HBsAg status is unknown** should receive Hep B within 12 hours of birth. Maternal blood should be drawn at delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). **All children and adolescents (through age 18 years)** who have not been vaccinated against hepatitis B may begin the series during any visit. Providers should make special efforts to vaccinate children who were born in or whose parents were born in areas of the world where hepatitis B virus infection is moderately or highly endemic.

§ The fourth dose of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) can be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. Tetanus and diphtheria toxoids (Td) is recommended at age 11–12 years if at least 5 years have elapsed since the last dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP), DTaP, or diphtheria and tetanus toxoids (DT). Subsequent routine Td boosters are recommended every 10 years.

¶ Three *Haemophilus influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If Hib conjugate vaccine (PRP-OMP) (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 months and 4 months, a dose at age 6 months is not required. Because clinical studies in infants have demonstrated that using some combination products may induce a lower immune response to the Hib vaccine component, DTaP/Hib combination products should not be used for primary vaccination in infants at ages 2, 4, or 6 months unless approved by the Food and Drug Administration for these ages.

** To eliminate the risk for vaccine-associated paralytic poliomyelitis (VAPP), an all-inactivated poliovirus vaccine (IPV) schedule is now recommended for routine childhood polio vaccination in the United States. All children should receive four doses of IPV: at age 2 months, age 4 months, between ages 6 and 18 months, and between ages 4 and 6 years. Oral poliovirus vaccine (OPV) (if available) may be used only for the following special circumstances: 1) mass vaccination campaigns to control outbreaks of paralytic polio; 2) unvaccinated children who will be traveling in <4 weeks to areas where polio is endemic or epidemic; and 3) children of parents who do not accept the recommended number of vaccine injections. Children of parents who do not accept the recommended number of vaccine injections may receive OPV only for the third or fourth dose or both; in this situation, health-care providers should administer OPV only after discussing the risk for VAPP with parents or caregivers. During the transition to an all-IPV schedule, recommendations for the use of remaining OPV supplies in physicians' offices and clinics have been issued by the American Academy of Pediatrics (*Pediatrics*, Vol. 104, No. 6, December 1999).

†† The second dose of measles, mumps, and rubella vaccine (MMR) is recommended routinely at age 4–6 years but may be administered during any visit, provided at least 4 weeks have elapsed since receipt of the first dose and that both doses are administered beginning at or after age 12 months. Those who previously have not received the second dose should complete the schedule no later than the routine visit to a health-care provider at age 11–12 years.

§§ Varicella (Var) vaccine is recommended at any visit on or after the first birthday for susceptible children, i.e., those who lack a reliable history of chickenpox (as judged by a health-care provider) and who have not been vaccinated. Susceptible persons aged ≥13 years should receive two doses given at least 4 weeks apart.

¶¶ Hepatitis A vaccine (Hep A) is recommended for use in selected states and regions. Information is available from local public health authorities and *MMWR*, Vol. 48, No. RR-12, October 1, 1999.

Use of trade names and commercial sources is for identification only and does not constitute or imply endorsement by CDC or the U.S. Department of Health and Human Services.

Source: Advisory Committee on Immunization Practices (ACIP), American Academy of Family Physicians (AAFP), and American Academy of Pediatrics (AAP).

Combination vaccine

- Several studies looking at the compatibility of HAV with MMR, Polio, HBV, Influenza.
- One study combines HAV and HBV in one vaccine
  - Twinrix (SmithKline) is a combination of Havrix and Engerix-B

Joines et al. A Prospective, comparative US trial of a combination hepatitis A and B vaccine (Twinrix) with corresponding monovalent vaccines (Havrix and Engerix-B) in adults. Vaccine 19 (2001) 4710-4719

Combination Vaccine

- In the study
  - 773 patients randomized to either Twinrix (n=414) or monovalent vaccines (n=415).
  - There was no difference in the two groups with regards to
    - Safety, side effects or immunogenicity

Vaccination
Special situations

- Patients with HCV infection
- Liver transplant patients
- Patients with cirrhosis

HCV Infection

- Infection with HAV in patients with chronic liver disease is associated with an increased frequency of fulminant hepatitis A
- CDC and NIH recommends vaccine for patients with HCV and those awaiting or who have received a liver transplant.

HCV Infection

- Vento et al. NEJM 1998
  - Followed 432 patients with chronic HCV for 82 months
  - 17 patients developed HAV.
    - 10/17 (59%) had uncomplicated courses
    - 7/17 (41%) developed fulminant hepatic failure
    - 6/7 fulminant cases were fatal.
- Cirrhosis was not present in the fatal cases on autopsy.

Characteristics of Seven Patients with Chronic Hepatitis C and HAV-Associated Fulminant Hepatitis

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (yr)	25	23	32	26	30	31	33
Sex	M	M	F	F	F	M	M
HLA phenotype	A1,3;B7,8;DR3	A1,2;B8,45;DR3,4	A1,19;B8,40;DR3,5	A2,19;B35,40;DR5,7	A1;B8,17;DR3,7	A3,11;B7,40;DR3	A19;B35,44;DR6,7
HCV genotype	2a	1b	1b	3a	1a	1a	2a
HGV infection	No	No	No	Yes	No	Yes	Yes
Histologic finding	CAH	CAH	CAH	CAH	CAH	CPH	CAH
Prothrombin time (INR)†	4.3	4.1	4.1	5.6	6.2	6.8	5.4
Serum ALT (U/liter)‡	3430	4100	3365	5176	8390	4764	8635
Serum gamma globulin (g/dl)	2.1	2.3	2.4	1.7	3.0	1.2	1.4
Antinuclear antibodies	1:80	1:40	1:80	Negative	1:640	Negative	1:20
Anti–smooth-muscle antibodies	1:320	1:320	1:640	Negative	1:640	Negative	Negative
Anti–asialoglycoprotein-receptor antibodies	1:800	1:400	1:1600	Negative	1:800	Negative	Negative
Outcome	Death	Death	Recovery	Death	Death	Death	Death

*CAH denotes chronic active hepatitis, CPH chronic persistent hepatitis, INR international normalized ratio, and ALT alanine aminotransferase.

†The normal range is 1 to 1.18.

‡The normal value is less than 38 U per liter.

Vento: N Engl J Med, Volume 338(5).January 29, 1998.286-290

HCV Infection

- Between 1983 and 1989 the CDC reported 115,551 cases of HAV
  - 107 fatalities in 2,311 cases with chronic liver disease
  - 247 fatalities in 113,009 patients without chronic liver disease
  - 4.6% vs 0.2% fatality rate in patients with pre-existing chronic liver disease.

HCV Infection

- The prevalence of HAV in the general population is 33%
- Patients with HCV have similar prevalence
- In a study of 671 patients with HCV*
  - 252 (38%) were HAV +
  - By age group
    - >60 y/o 76% prevalence
    - 40-60 y/o had 34% prevalence
    - <40 y/o had 21% prevalence

*Siddiqui et al. Prevalence of Hepatitis A Virus and Hepatitis B Virus Immunity in patients with Polymerase Chain Reaction-Confirmed Fepatitis: Implications for Vaccination Strategy. *AM J of Gastroenterology*.

HCV Infection

- Vaccination strategy
  - Age group less than 40
    - Empiric vaccination with one dose is cost-effective ($96.00).
    - If two doses are used, check the Ab first ($36.00)
  - Age group > 60 y/o
    - Check the antibody, if negative, then vaccinate

Liver Transplant Recipients

- Arslan et al. Transplantation July 2001
  - 37 patients s/p transplant that were HAV seronegative
  - 45 patients in an unvaccinated control group
    - 3 of 37 (8%) patients converted at 1 month
    - 5/26 (26%) patients converted at 6 months
    - 6 of 23 (26%) converted at 7 months
  - No serious side effects

Liver Transplant Recipients

- Vaccination against HAV in OLT recipients is safe and well tolerated.
- Seroconversion in this population is not optimal
  - Possibly due to immunosuppression.
    - Responders were further from transplant (>75 months) than non-responders

Cirrhosis

- HAV vaccination is recommended in patients with cirrhosis
- Arguedas et al. Hepatology July 2001
  - 84 patients with cirrhosis who were HAV negative were divided in 2 groups
    - Group 1: 49 patients with compensated liver disease (Child-Pugh class A)
    - Group 2: 35 patients with decompensated liver disease (Child-Pugh class B & C)

Cirrhosis

- All patients received vaccination with a booster at 6 months
  - Group 1
    - 35/49 (71.4%) responded at 1 month
    - 48/49 (98%) responded with the second dose
  - Group 2
    - 13/35 (37%) responded at 1 month
    - 23/35 (66%) responded with the second dose

Cirrhosis

- Response to HAV vaccination in chronic liver disease is optimal when targeted to patients before development of hepatic decompensation
- Vaccinate patients early

Post-Exposure Prophylaxis

- Serum IG within 2 weeks of exposure
  - 0.02 ml/kg IM
- Side effects include
  - Fever, myalgias and pain at the site
- Levels are not detectable by commercially available tests
- Usually accompanied by immunization

TABLE 4. Recommended doses of immune globulin (IG) for hepatitis A preexposure and postexposure prophylaxis*

Setting	Duration of Coverage	IG Dose†
Preexposure	Short-term (1–2 mos)	0.02 mL/kg
	Long-term (3–5 mos)	0.06 mL/kg§
Postexposure	—	0.02 mL/kg

*Infants and pregnant women should receive a preparation that does not include thimerosal.
†IG should be administered by intramuscular injection into either the deltoid or gluteal muscle. For children <24 months of age, IG can be administered in the anterolateral thigh muscle.
§Repeat every 5 months if continued exposure to HAV occurs.

Conclusions

- HAV is a widespread infection without reservoirs.
- Currently vaccination is targeted towards groups at increased risk
  - These respond to vaccination early in the course of their disease